

HUBR-1206 (10202655)

REMARKS

Reconsideration of this application, as amended, is respectfully requested.

Claim 39 has been amended to overcome the objections thereto.

All claims were rejected either as anticipated by Ulrich alone or as obvious over Ulrich in view of secondary references. Applicants respectfully traverse each of these rejections.

The concept of the sustained release form according to the presently claimed invention is discussed below.

An object of the present invention was to provide a sustained release form enabling the controlled and improved release of  $\alpha$ -lipoic acid or an  $\alpha$ -lipoic acid derivative.

This object has been achieved with the claimed sustained release form made of

- (a) one or more cationogenic polymers,
- (b)  $\alpha$ -lipoic acid and/or a derivative thereof and
- (c) at least one acid different from (b)

as presently claimed.

The sustained release form comprising the three above defined components (a), (b) and (c) enables a retarding adhesion of the active substance on the basis of ionic, dipolar as well as other intermolecular interactions between the components. Figure 1 of the specification illustrates these interactions between the cationogenic polymer (a) (e.g. chitosan), the anionogenic  $\alpha$ -lipoic acid component (b) and the further acid component (c). It has to be noted that both components (a) and (c) are not merely regarded as trivial components or auxiliary agents for formulation; rather, they are essential for the invention and play a considerable role with respect to the sustained release of the active ingredient.

On page 13, the paragraph labeled "1. diffusion study", explains in detail that even low concentrations of the acid component (c) bring about an increased effect of the cationogenic polymer (chitosan) sustaining the release of the active ingredient  $\alpha$ -lipoic acid. The rate of

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release of  $\alpha$ -lipoic acid out of the retard complex is significantly reduced, even if only few amino groups of the cationogenic polymer are occupied with the anionogenic acid component. This is due to an increase in free primary amino groups in the cationogenic polymer, which are accessible to the  $\alpha$ -lipoic acid component; this is attributable to the higher degree of hydration, caused by the acid component. As soon as a certain acid concentration is reached in the retard complex and all the primary amino acid groups of the cationogenic polymer are accessible to the active ingredient, the maximum of the release-sustaining effect is achieved.

These mechanisms are also reflected in the method of preparing the sustained release form according to claim 44. In this method, the first process step is mixing component (a) with component (c) before the obtained mixture is homogenized with the  $\alpha$ -lipoic acid component (b). To achieve the desired sustained release effect, it is necessary that first the cationogenic elements of the polymer component are at least partially covered by the additional acid component.

The benefit of the sustained release form according to the present application thus is a controlled release of active ingredients for more than about 8 hours, an improved absorption of the  $\alpha$ -lipoic acid or derivatives thereof for example from the gastrointestinal tract, and thus an improved bioavailability of the  $\alpha$ -lipoic acid or derivatives thereof.

Ulrich describes compositions comprising dehydrolipoic acid or salts thereof. According to Ulrich, numerous components of different kind are listed that can be further contained in the compositions as auxiliary substances, antioxidants, preservatives etc. (column 6, line 65 to column 9, line 18).

In the bridging paragraph of column 6 and 7 for example, ascorbic acid, gallic acid, phosphoric acid and benzoic acid are mentioned. The same are however added as antioxidants and do not lead to any interactions with polymers as required for the sustained release mechanism according to the invention. Furthermore, an interaction of the antioxidant acids described in Ulrich with other ingredients would strongly limit their actual purpose, i.e. the protection of antioxidant influences and thus affects the whole formulation negatively.

Further, an extensive list of carriers and auxiliary substances of different kind can be gathered from the text passages cited by the Examiner (column 7, line 34 to column B, line 47).

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Among these numerous compounds, however, only very few compounds e.g. Eudragit products, can be classified as belonging to the group of the cationogenic polymers according to the invention.

At column 6, lines 63-64 of Ulrich, a general indication is given that the application is possible in sustained release and non-sustained release form, however, no concrete and reproducible guidance is provided for achieving a sustained release form. From the mere enumeration of compounds in Ulrich, no hint can be taken concerning the sustained release form according to the present invention comprising the active ingredient  $\alpha$ -lipoic acid and both a cationogenic polymer and at least one further acid component. Ulrich neither discloses nor renders obvious cationogenic polymers per se, their meaning for the sustained release effect nor any interaction between the cationogenic polymers and anionogenic compounds.

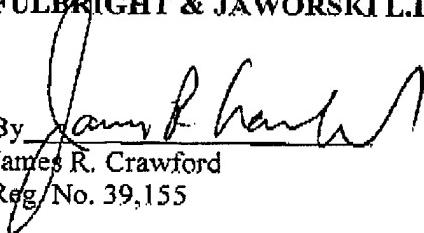
Thus, Ulrich does not anticipate nor render obvious the claimed invention.

In view of the foregoing, it is respectfully requested that all rejections be withdrawn.

Any fees necessary to enter this amendment may be charged to deposit account no. 50-0624.

Respectfully submitted,

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